TrisKem International

vUGM

part of the NPL vCARM conference

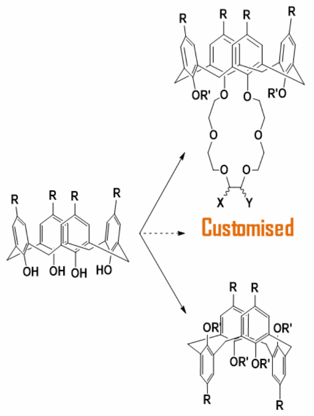
News Radiopharmacy and other on-going R&D

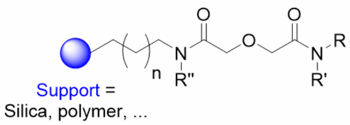
S. Happel - 24/11/2020

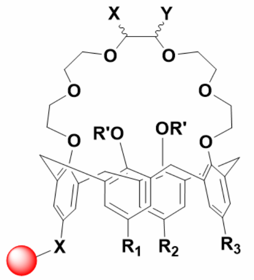
TRISKEM
Expertise in Separation Chemistry

R&D TrisKem International

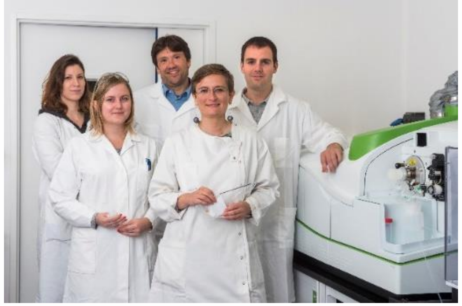
- R&D , TechSupport & QC team: 9 persons
  - ➢ 3 radiochemistry PhD, 2 organic chemistry PhD, 4 technicians
- Two R&D labs:
  - – Synthesis Lab (new resins and extractants)
    - Incl. grafted resins (silica or polymers), macrocycles,…
    - Extractants
  - – Application Lab
    - Preparation of extraction chromatographic resins
    - Resin characterisation and method development



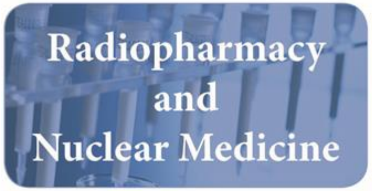




- Counting equipment:
  - – ICP-MS, IC, TOC, TGA, IR, moisture analyzer, surface area analyser, particle size and shape analyser, pycnometer
  - – Production and packing lab with four 20L reactors
- No handling of radioactivity => R&D cooperation
  - – Resin and method development “cold” => R&D partner



R&D interest in Radiopharmacy



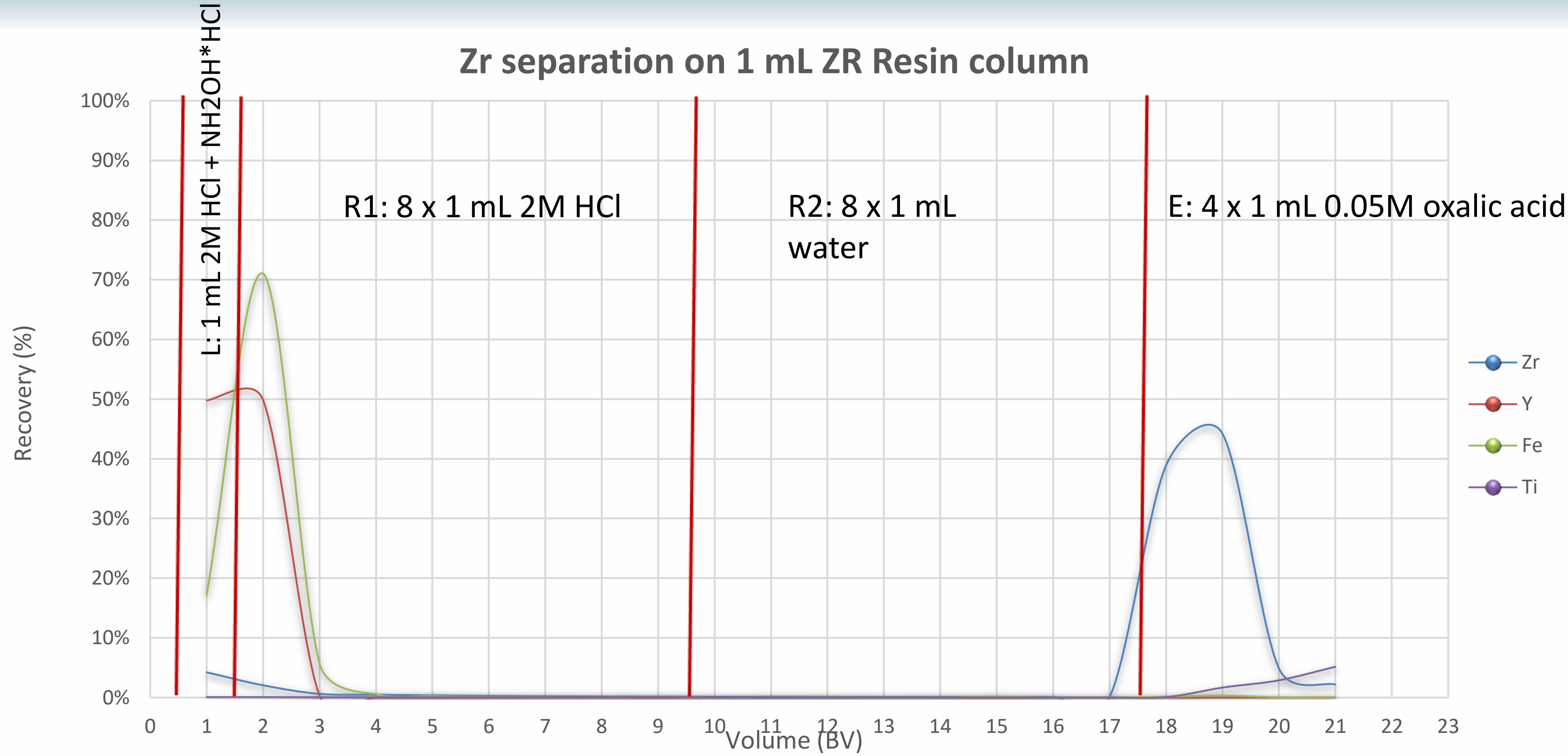
- Radionuclide production
  - Separation of radionuclides from irradiated targets
    - » Diagnostics: Zr-89, Cu-64, Ga-68, Ge-68, Ti-44/5, Tc-99m, Sc-43/4,…
      - **ZR Resin, CU Resin, TK200 Resin, TK400, TK201, TK202,…**
    - » Therapy: alpha emitters, Lu-177, Tb-161 Cu-67, Sn-117m, Sc-47,…
      - **TK400, TK200, TBP Resin, CU Resin, TK211/2/3, TK221,…**
- Quality control
  - **DGA sheets** (functionalized TLC, Ra-223, Ga-68, Pb-212,….
    => CVUT Prague)
  - Cartridge based methods
- Decontamination of effluents
- Purification of generator eluates => under development

A scheme of chromatographic separaton of mixture of ^{227}Ac and his daugther´s niclides. ^{227}Th remains on start, ^{227}Ac has the retenton factor ca 0.2, ^{211}Pb ca 0.7 and ^{223}Ra ca 0.9.

Zr-89 separation

- ZR Resin
  - Hydroxamate based resin => different from Holland publication!
  - Standard for Zr separation from Y targets
  - Ready to use / no activation
  - Facile Zr elution (avoid 1M oxalic acid)
- Zr-89 production via (p,n) reaction from ^{nat}Y targets
  - High Zr/Y selectivity necessary
  - Alternative e.g. TBP Resin (=> Graves et al.)
- Application for other separations: **Ti/Sc**, **Ga/Zn, Ge/Ga**

Zr-89 separation on ZR Resin



- No activation with acetonitrile!
- Load preferably from 2M HCl
- Rinsing described by Holland may be employed (2M HCl / water)
- Clean Fe removal
- Quantitative Zr elution in 1.5 - 2 mL ≥ 0.05M oxalic acid
- Oxalic acid conc. may be higher (e.g. 1M) => smaller elution volume
- For ≤ 100mg Y often 0.3mL ZR Resin

Zr-89 separation on TBP Resin

TRISKEM
Expertise in Separation Chemistry

- Method published by Graves et al.
- 400mg Y foils irradiated at 14 MeV (50 µA)
- Dissolution in 10 mL conc. HCl
- Separation on 220 mg TBP Resin
- Load from 9.6M HCl, rinse with 20 mL 9.6M HCl
- Zr elution with 1 mL 0.1M HCl
- Zr yield: 89 ± 3%, Y decontamination: 1.5 x 10^5
- Zr elution should also be possible with oxalate, citrate, phosphate…
- Other applications of TBP Resin:
  - Sc isotope production from Ca targets (=> presentation EANM'18, Polatom)
  - Sn-117m from Cd targets

ELSEVIER
Nuclear Medicine and Biology
Volumes 64–65, September–October 2018, Pages 1-7

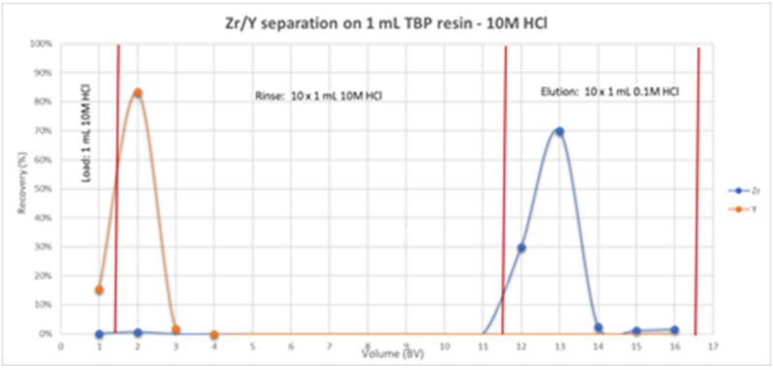
Evaluation of a chloride-based ^{89}Zr isolation strategy using a tributyl phosphate (TBP)-functionalized extraction resin

Stephen A. Graves [a], Christopher Kutyreff [b], Kendall E. Barrett [b], Reinier Hernandez [c], Paul A. Ellison [b], Steffen Happel [d], Eduardo Aluicio-Sarduy [b], Todd E. Barnhart [b], Robert J. Nickles [b], Jonathan W. Engle [b]

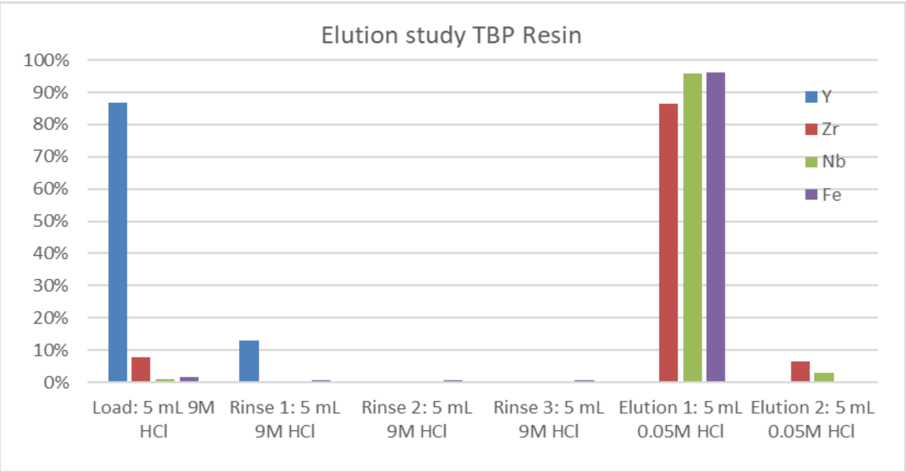
Show more

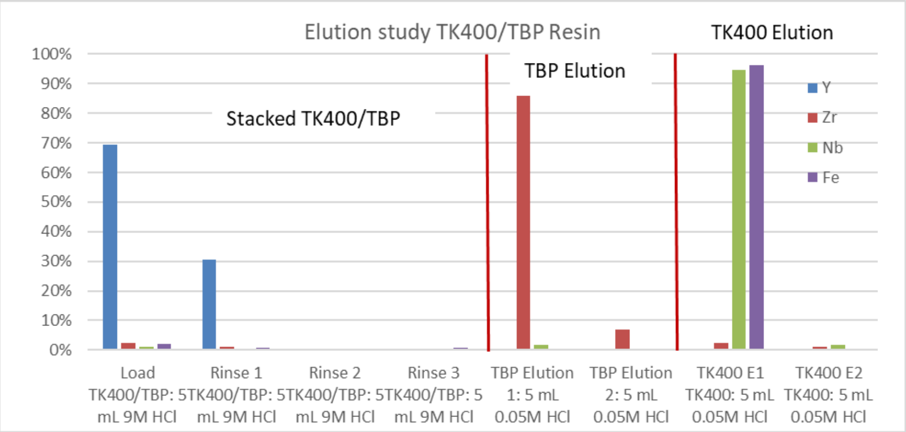
https://doi.org/10.1016/j.nucmedbio.2018.06.003

Get rights and content



Use of TK400 for Fe/Nb removal

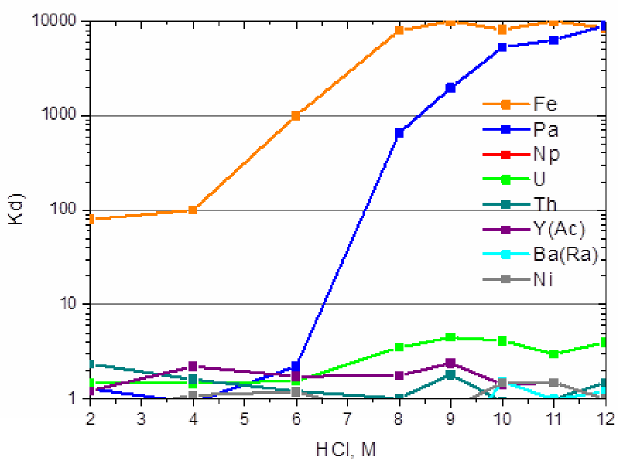




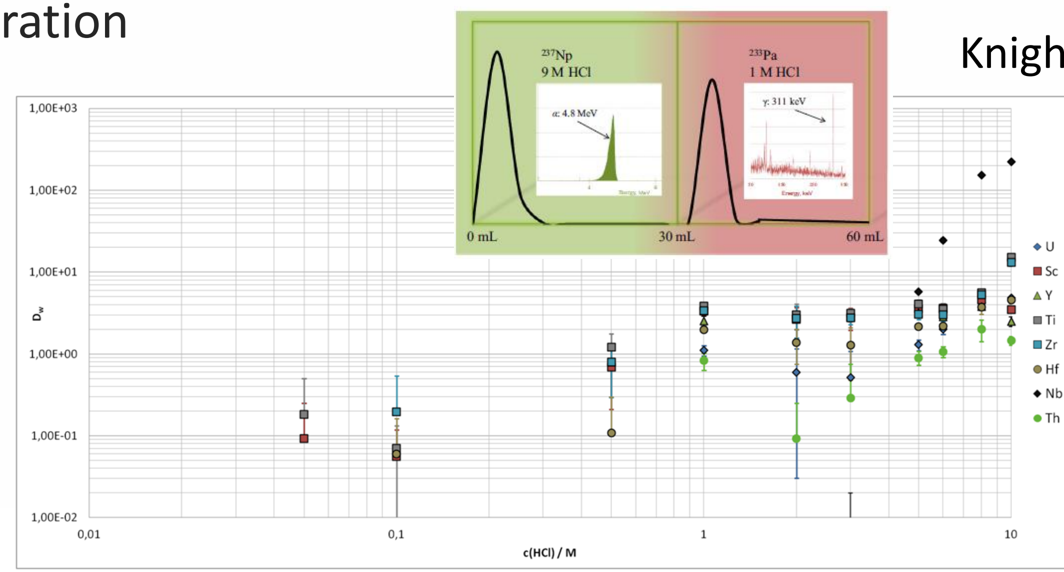
- On-going work following questions about Fe removal
  - On TBP only: Fe and Nb follow Zr
- Removal of Fe & Nb upfront possible using TK400 Resin
- Test with stacked 2 mL TK400/TBP cartridges
  - Load and Rinse: TK400 stacked above TBP
  - Elution: splitting of cartridges and separate elution
    - TBP => ZR
    - TK400 = > Fe & Nb
- Best results:
  - TK400 run at 9M HCl => no Zr retention
  - Adjustment of eluate to ≥ 10M HCl
  - Loading of adjusted eluate onto TBP for Zr purification

TK400 Resin

- Long chained alcohol
- Retention only at high HCl concentration, elution in low HCl, water,…
- Main application: Pa separation (Pa-231 determination by MS/Pa-230 for medical use)
  - NPL (no selectivity for actinides, Ac, Ra, Pb,…=> Pa-230 purif.)
- Other applications:
  - Also retains Mo, Fe, Ga, Po (=> SR Resin!)
  - Nb separation from Zr possible (Nb-90)
  - Under testing for At separation



Knight et al.



Ti-44/Sc-44

Separation of ^{44}Ti from proton irradiated scandium by using solid-phase extraction chromatography and design of ^{44}Ti/^{44}Sc generator system

V. Radchenko, C.A.L. Meyer, J.W. Engle, C.M. Naranjo, G.A. Unc, T. Mastren, M. Brugh, E.R. Birnbaum, K.D. John, F.M. Nortier, M.E. Fassbender *

Chemistry Division, Los Alamos National Laboratory, P.O. Box 1663, Los Alamos, NM 87545, USA

TRISKEM
Expertise in Separation Chemistry

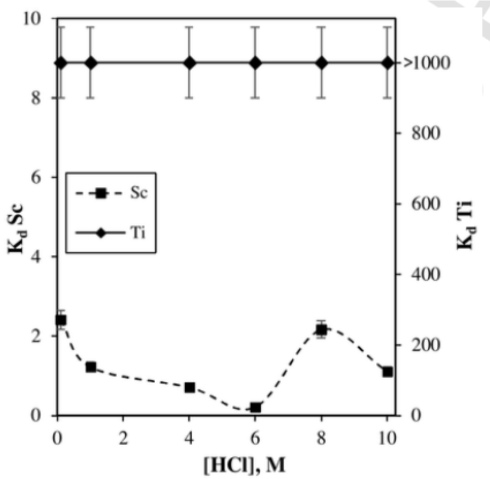


Fig. 3. HCl concentration dependency of K_d for ^{44}Ti/^{46}Sc on ZR hydroxamate resin.

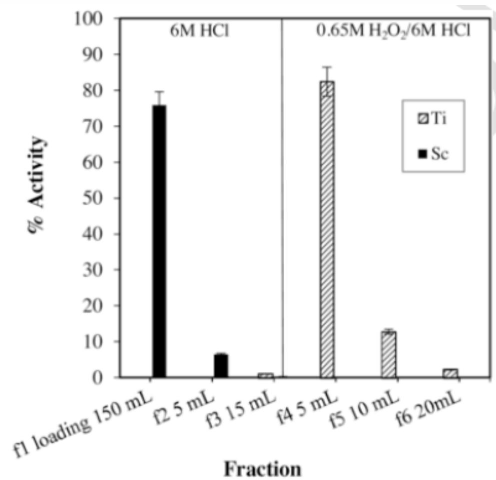


Fig. 5. ^{44}Ti/^{46}Sc elution profile using ZR hydroxamate resin with a load of 4 g of scandium.

➢ **Ti-44 production**
- 4g irradiated Sc
- 5 mL Zr Resin
- Ti-44 yield >95%
- 65.2 MBq Ti-44
- D_f(Sc): 10^5

Ti-45 => K. Olguin presentation

Use of ZR Resin as support in Ti-44/Sc-44 generators

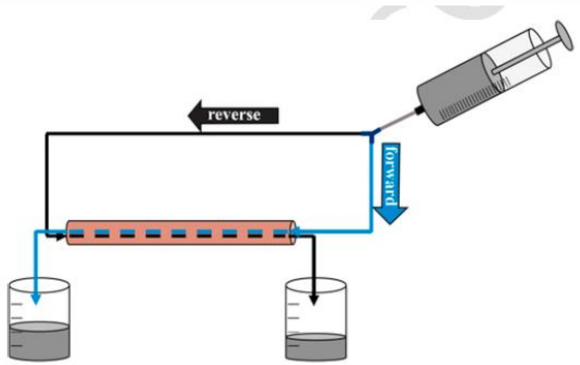


Fig. 1. Schematic concept of a forward/reverse flow radionuclide generator.

- Direct (1 mL ZR) and reverse elution (2 mL ZR)
- 65 column volumes tested up until publication
- High Sc yields, max. Ti-44 breakthrough: $4.1 \cdot 10^{-4}$%
- Obtained Sc gave labelling yields > 94%

➢ Generator been set-up at BNL/SBU => Poster S. Houclier ISRS 2019

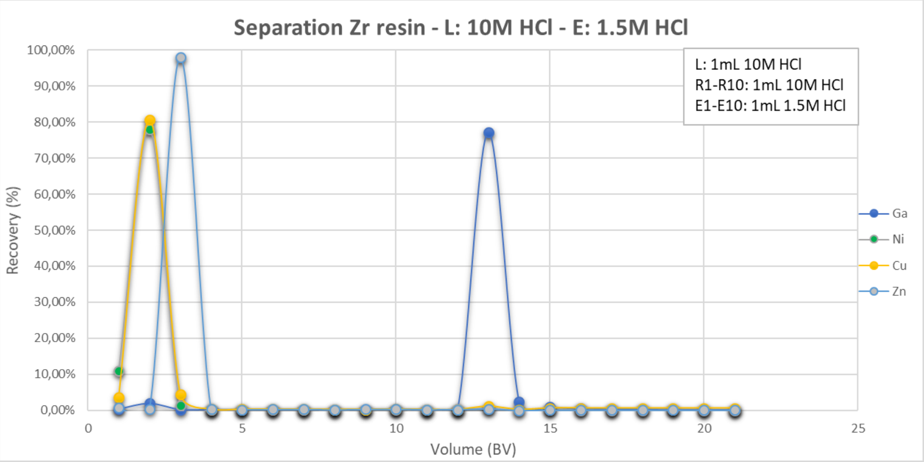
Ge-68 separation from GaNi or GaCo

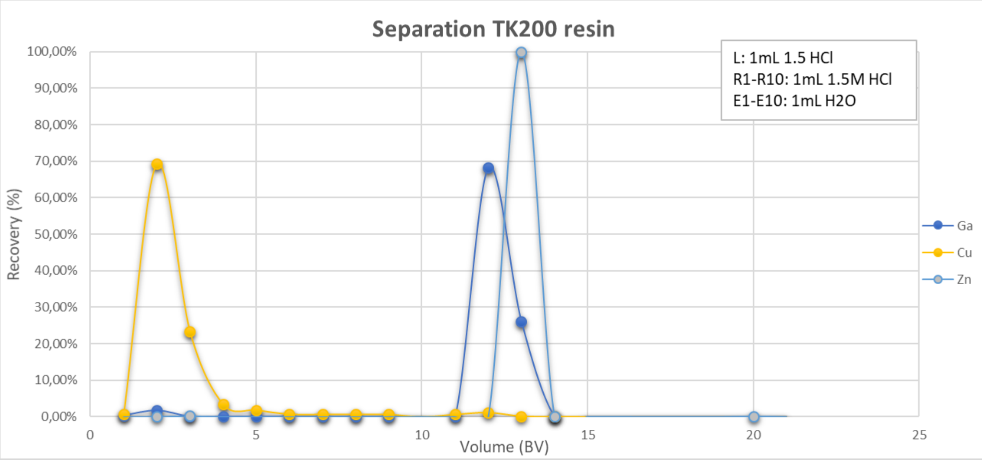
- Loading from HNO_3, HCl or H_2SO_4
  - Target dissolution in HNO_3 or $\mathbf{H_2SO_4}$ often preferred => $GeCl_4$ volatile
- On-going: Cold test on >5g GaNi
- First cycle on ZR Resin
  - 2 mL ZR Resin cartridge
  - Load/rinse from 5M H_2SO_4
  - High Ge retention/purification from Ga, Ni & Co
  - Elution: 0.1M citric acid (pH 3)
  - Preferably at ≤ 1 mL/min
- Second cycle on ZR Resin
  - Preferably 1 mL cartridge
    - Alternative 2 mL cartridge
  - Adjustment of eluate to 5M H_2SO_4
  - Load of adjusted eluate through ZR
  - Rinse with 5M H_2SO_4
  - Elution with 0.1M citric acid (pH 3)
  - Preferably at ≤ 1 mL/min
- Conversion step (citric acid to HCl):
  - Acidification to 9M HCl, load onto Guard Resin
    - Alternatives: Prefilter or TK400
    - Advantage Guard Resin: further Ga removal
    - Advantage Prefilter/TK400: works at 6M HCl - but no selectivity for Ge over Ga
  - Rinse with 9M HCl
  - Elution with 0.05M HCl => pH control!
- Overall very high Df & chemical yield

Ga-68(/Ga-67) separation from Zn targets

- **ZR Resin**
  - Loading possible from:
    - dilute HNO_3 (**liquid targets**)
    - > 6M HCl (**solid targets**)
  - Rinse under loading condition
  - Ga separation on ZR Resin
  - Elution with ~1.5M HCl

- **Ga conversion step on TK200**
  - TK200 load from 1.5M HCl
  - Rinse with 1.5M HCl
    - Better pH control of eluate via rinse with NaCl/HCl before elution=> Gagnon et al.
  - Elution in 2 – 3 BV water





⇒ **New IAEA TechDoc:**
https://www-pub.iaea.org/books/IAEABooks/13484/Gallium-68-Cyclotron-Production

Cyclotron production of Ga-68

TRISKEM
Expertise in Separation Chemistry

Rodnick et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:25
https://doi.org/10.1186/s41181-020-00106-9

EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Cyclotron-based production of ^{68}Ga, [^{68}Ga]GaCl$_3$, and [^{68}Ga]Ga-PSMA-11 from a liquid target

Melissa E. Rodnick[1], Carina Sollert[2], Daniela Stark[3], Mara Clark[1], Andrew Katsifis[3], Brian G. Hockley[1], D. Christian Parr[2], Jens Frigell[2], Bradford D. Henderson[1], Monica Abghari-Gerst[1], Morand R. Piert[1], Michael J. Fulham[4], Stefan Eberl[5*], Katherine Gagnon[2*] and Peter J. H. Scott[1*]

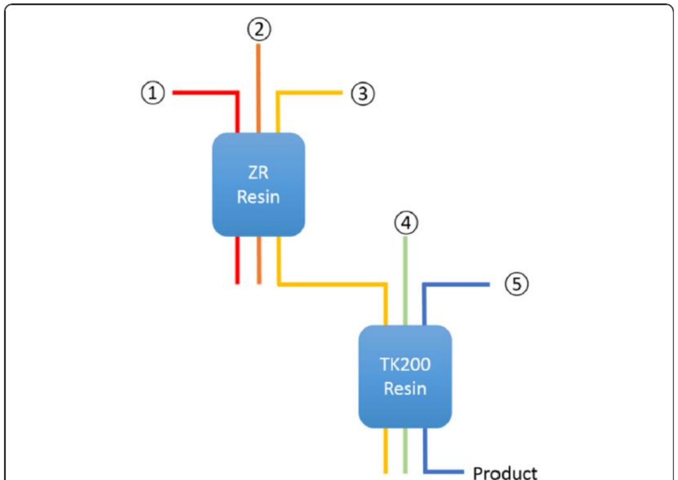


Fig. 4 Two-column approach for ^{68}Ga chemical separation

Table 1 High level schemes of [^{68}Ga]GaCl$_3$ purifications

	Scheme A*	Scheme B
① ZR Load	< 0.1 M HNO_3	
② ZR Wash	15 mL 0.1 M HNO_3	
③ ZR Elution / Trapping on TK200	5–6 mL ~ 1.75 M HCl	
④ TK Wash	–	3.5 mL 2.0 M NaCl in 0.13 M HCl
⑤ TK Elution	H_2O	1–2 mL H_2O followed by dilute HCl to formulate

*Process as reported previously (Nair et al. 2017)

- J. Kumlin et al. (preprint):
  - ZR, LN & TK200 for solid targets

ORIGINAL RESEARCH

Multi-Curie Production of Gallium-68 on a Biomedical Cyclotron and Automated Radiolabelling of PSMA-11 and DOTATATE

Helge Thisgaard, Joel Kumlin, Niels Langkjær, Jansen Chua, Brian Hook, Mikael Jensen, Amir Kassaian, Stefan Zeisler, Sogol Borjian, Michael Cross, Paul Schaffer, Johan Hygum Dam

DOI: 10.21203/rs.3.rs-70698/v1 Download PDF

  - High Ga-68 activities
  - ARTMS/Odense: 10 Ci production: https://physicsworld.com/a/cyclotron-based-gallium-68-generator-breaks-production-records/
- W. Tieu et al.: Use of single TK400 cartridge for solid Zn targets

ELSEVIER
Nuclear Medicine and Biology
Volumes 74–75, July–August 2019, Pages 12-18

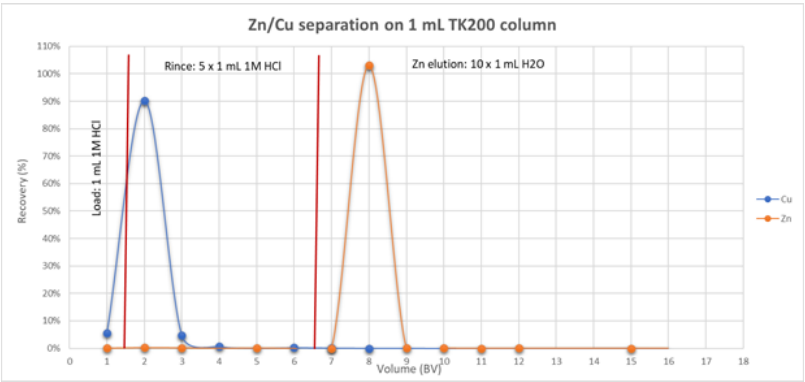
Rapid and automated production of [^{68}Ga]gallium chloride and [^{68}Ga]Ga-DOTA-TATE on a medical cyclotron

William Tieu, Courtney A. Hollis, Kevin K.W. Kuan, Prab Takhar, Mick Stuckings, Nigel Spooner, Mario Malinconico

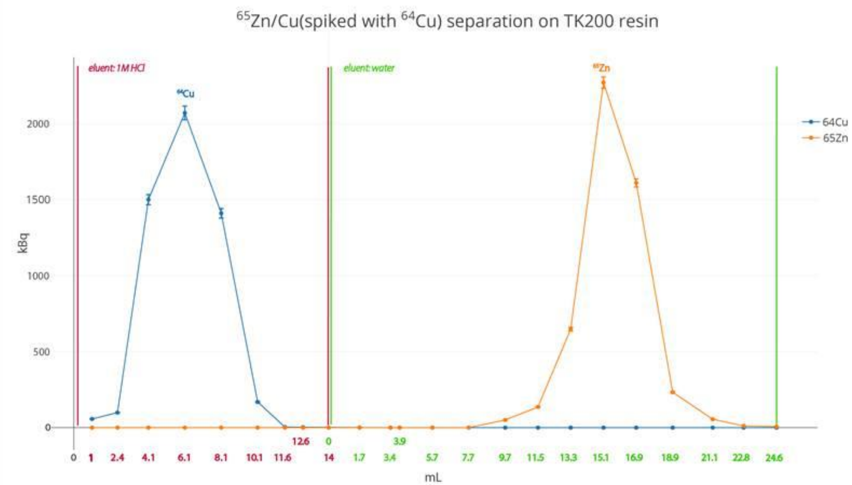
Other examples for separations on TK200 (TOPO based)

TRISKEM Expertise in Separation Chemistry

- Zn separation from Cu

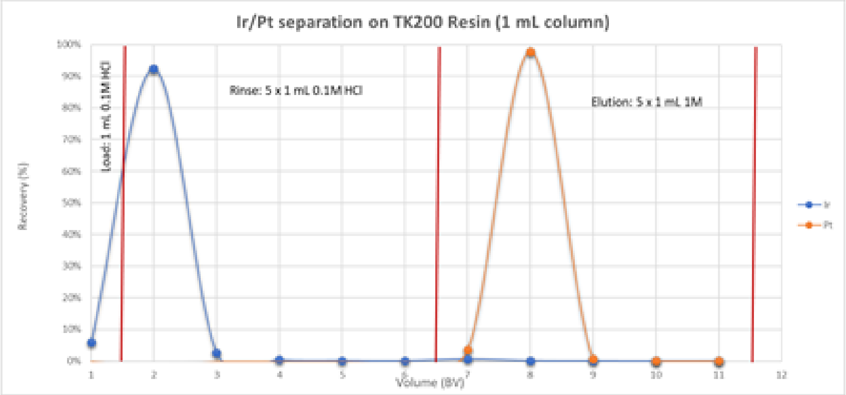


- Zn/Cu separation. Elution study, ICP-MS measurement



- Zn-65 separation. Data kindly provided by Fedor Zhuravlev, DTU

- Pt separation from Ir

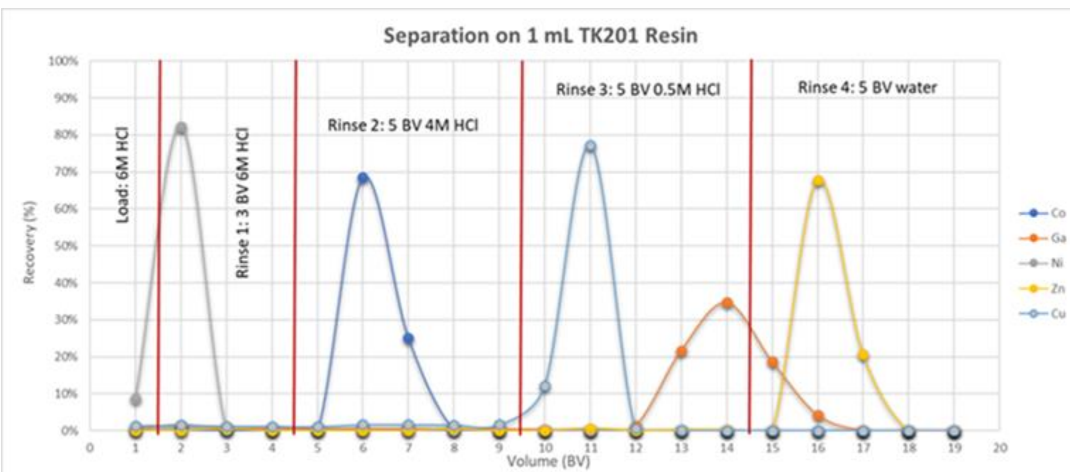


- Pt/Ir separation. Elution study, ICP-MS measurement

- Other systems under testing
- Radioanalysis: actinide separation
- Tri and tetravalents generaly more difficult to elute (Sc,…)

Cu-61/4 separation on TK201

- Cu-64 separation from solid Ni targets on TK201:
  - Load and rinse at 6M HCl => Ni removal => recovery/recycling
  - Co elution with 4 – 5M HCl
  - Gagnon et al. use of NaCl/HCl for better pH control of eluate
  - Cu elution with 0.5M HCl => Fe and Zn remain retained
  - Preferred alternative: Use of TBP (or TK400) upfront for Fe/Ga removal => allows for Cu elution in 0.05M HCl



Svedjehed et al. EJNMMI Radiopharmacy and Chemistry (2020) 5:21
https://doi.org/10.1186/s41181-020-00108-7
EJNMMI Radiopharmacy and Chemistry

RESEARCH ARTICLE Open Access

Automated, cassette-based isolation and formulation of high-purity [^{61}Cu]$CuCl_2$ from solid Ni targets

Johan Svedjehed[1], Christopher J. Kutyreff[2], Jonathan W. Engle[2,3] and Katherine Gagnon[1*]

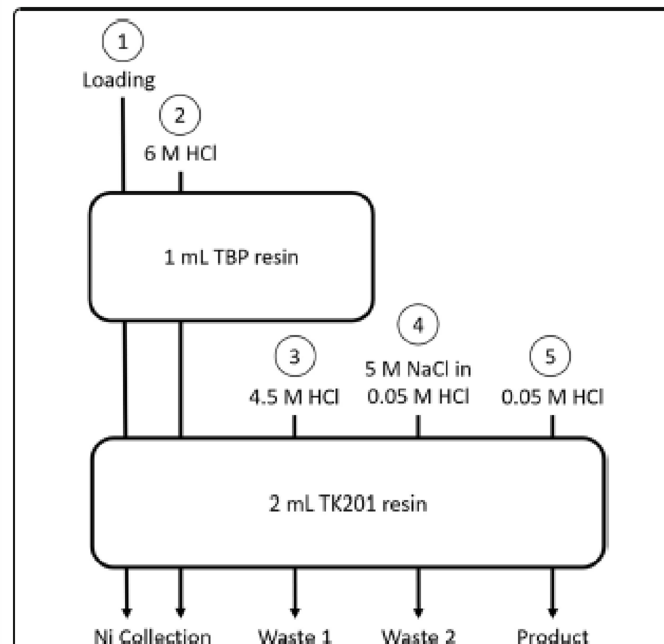


Fig. 1 Two-column approach for ^{61}Cu separation. Process steps described below

Cu-67 at BNL (DeGraffenreid et al.)

TRISKEM
Expertise in Separation Chemistry

Purification of ^{67}Cu and Recovery of its Irradiated Zn Target

A.J. DeGraffenreid[a], R. Nidzyn[a], B. Jenkins[a], D.E. Wycoff[b], T.E. Phelps[b], A. Goldberg[a], D.G. Medvedev[a], S.S. Jurisson[b], C.S. Cutler[a]
[a]Brookhaven National Laboratory, C-AD/MIRP—Upton, NY (USA)
[b]University of Missouri, Department of Chemistry—Columbia, MO (USA)

Poster presented at ISRS 2017

- 13.7g Zn metal dissolved to give 312 mg $ZnCl_2$/mL solution at pH 2
- Loading of 60,6 mL => 18.9g ZnCL2 onto 2.4g CU Resin column => 8 mL
- Rinse with 80 mL pH2 HCl
- Elution in 2 x 20 mL 6M HCl
- Evaporation to dryness
- Chemical yield ~100%
- Single column D_f for Zn ~10 000
  - Additional removal indicated
- Ideally further Zn and Co removal
- Original suggestion: AIX

Cu Resin

Nuclide	EOB Activity (mCi ± 1σ)	Recovery (%) Load w/ Quant. Transfer	pH 2 HCl Rinse	Acid #1	Acid #2
^{64}Cu	4700 ± 200	ND	ND	102	ND
^{65}Zn	41.0 ± 0.8	103	ND	0.04	ND
^{58}Co	63 ± 1	104	0.04	0.1	0.01

- Produced 143 mCi ^{67}Cu
- Quantitative recovery of radiocopper
- 99.5% radionuclidic purity—single column
- ICP-OES: 132.9 µg Cu and 1.3 mg Zn
  - Anion exchange column still needed to remove trace Zn
- Specific activity ^{67}Cu at EOB: 1.07 mCi/µg

Cu Resin

Robust separation that could shorten the overall processing time to separate co-produced radionuclides and large quantities of Zn from radiocopper
Cation and anion exchange columns still needed to suitably purify radiocopper

Alternatives to AIX:

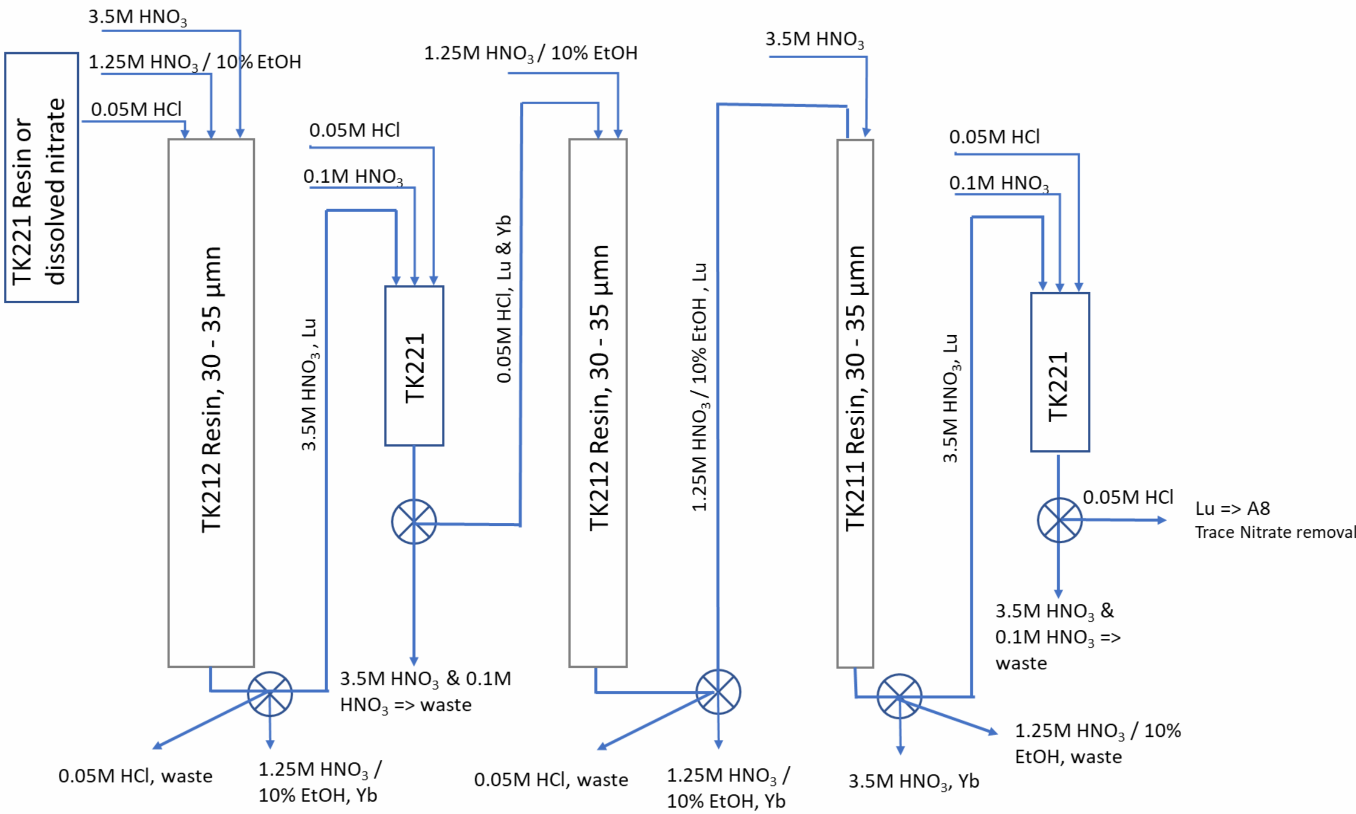
- TK201: prefered option. Cu elution from CU Resin with 6M HCl directly onto TK201, followed by Cu elution from TK201 in dilute acid
- TK200: Cu eluted from CU Resin in 1 - 2M HCl, direct load through TK200 (Zn retained, Cu passes)

• On-going developments radiolanthanides (nca Lu-177, Tb-161)

TRISKEM
Expertise in Separation Chemistry

- Separation of nca Lu-177 from Yb-176 targets (500 – 2000 mg)
- Partial simplification via sequential separation steps
  - 'Sequential separations' approach also applicable e.g. to Tb separation
- New resins: TK211/2/3
  - On-bead mix of different extractants for improved selectivity
  - Higher extractant load
  - Small amount of long-chained alcohol and use of inert support containing aromatic groups => aim: improved radiolysis stability
  - 20 - 50 µm beads
    - Originally developped as 15µm beads => too small for large scale separations
  - Resins also applicable to Horwitz method
    - TK212 & TK221 instead of LN2 and DGA
- Prepacked PP columns under development
  - 29 mL, 53 mL, 150 mL, 375 mL and 750 mL
  - With CoA
- Upscale to 1g and 2g Yb targets under finalisation

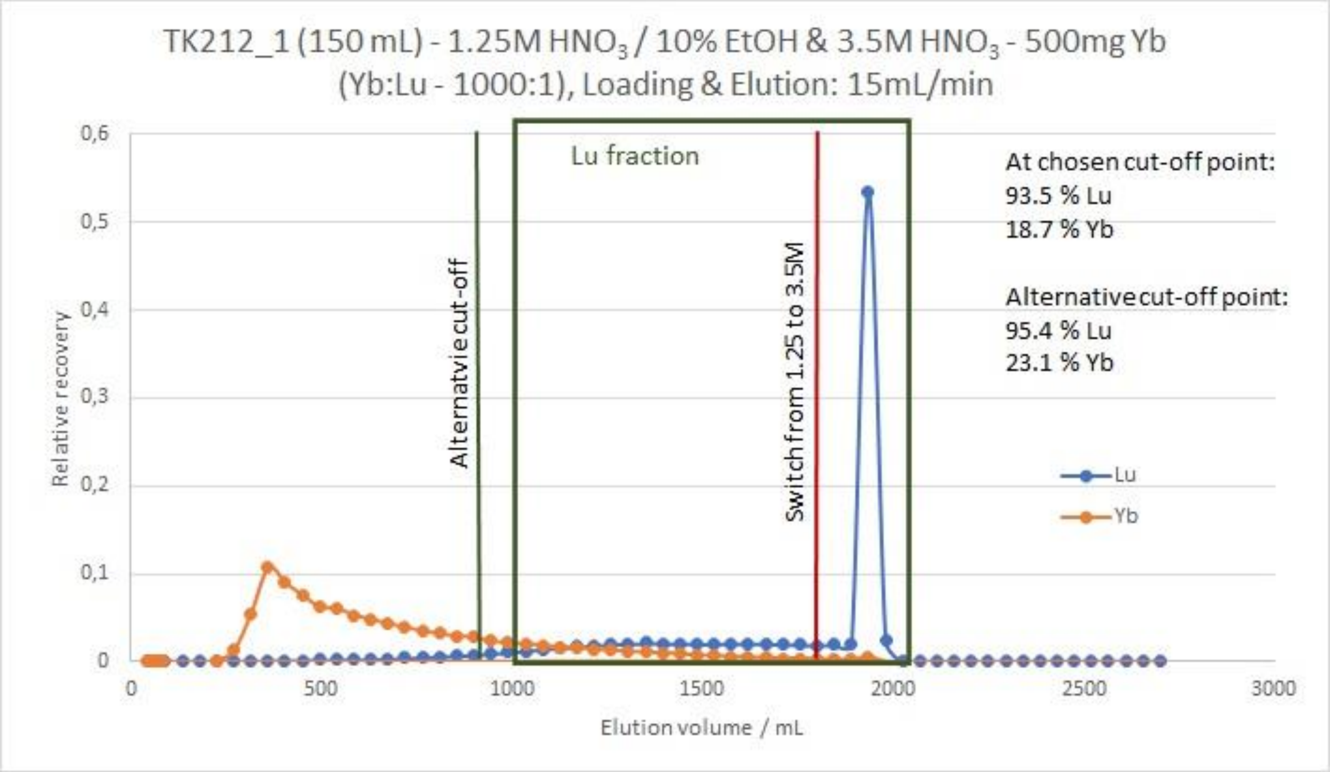
• Simplified method for Lu separation from 500 mg Yb – TK211/2 & TK221



- Partial simplification via sequential separation step (direct load from TK212 onto TK211 for polish)

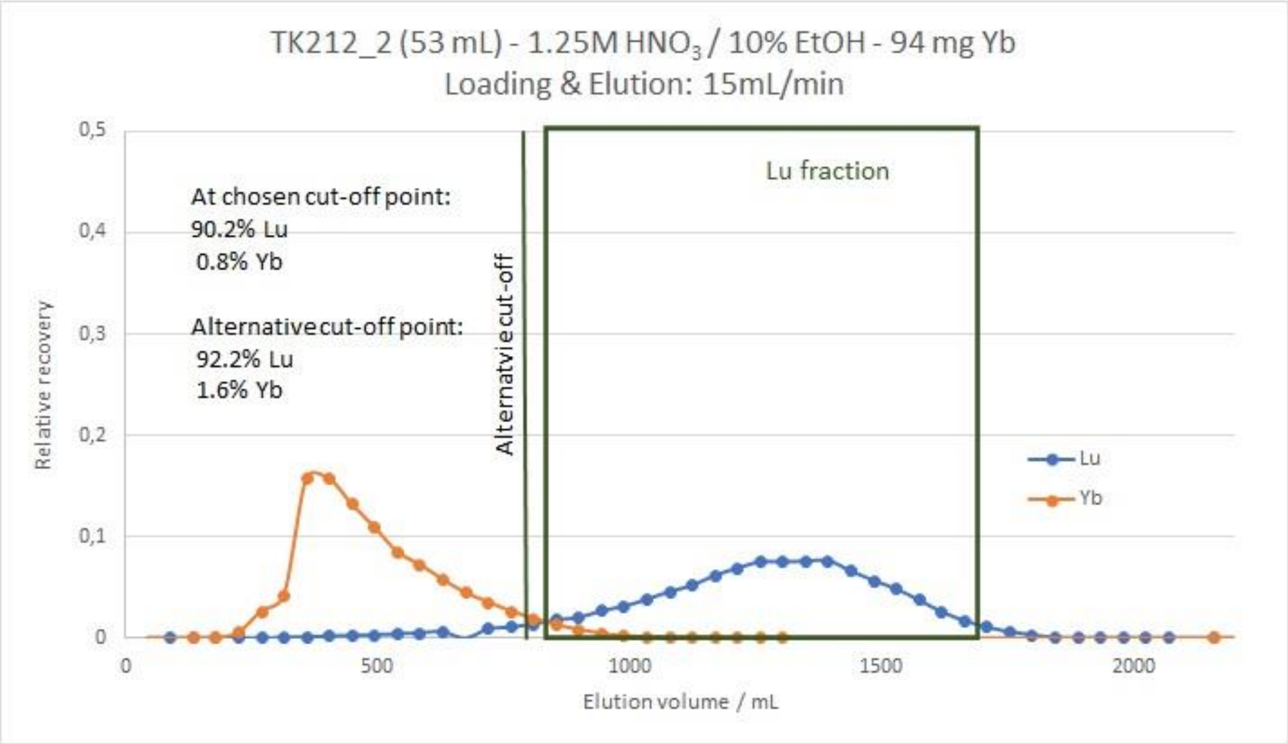
Lu separation form 500 mg Yb - **TK212**/TK221/TK212/TK211

TRISKEM
Expertise in Separation Chemistry



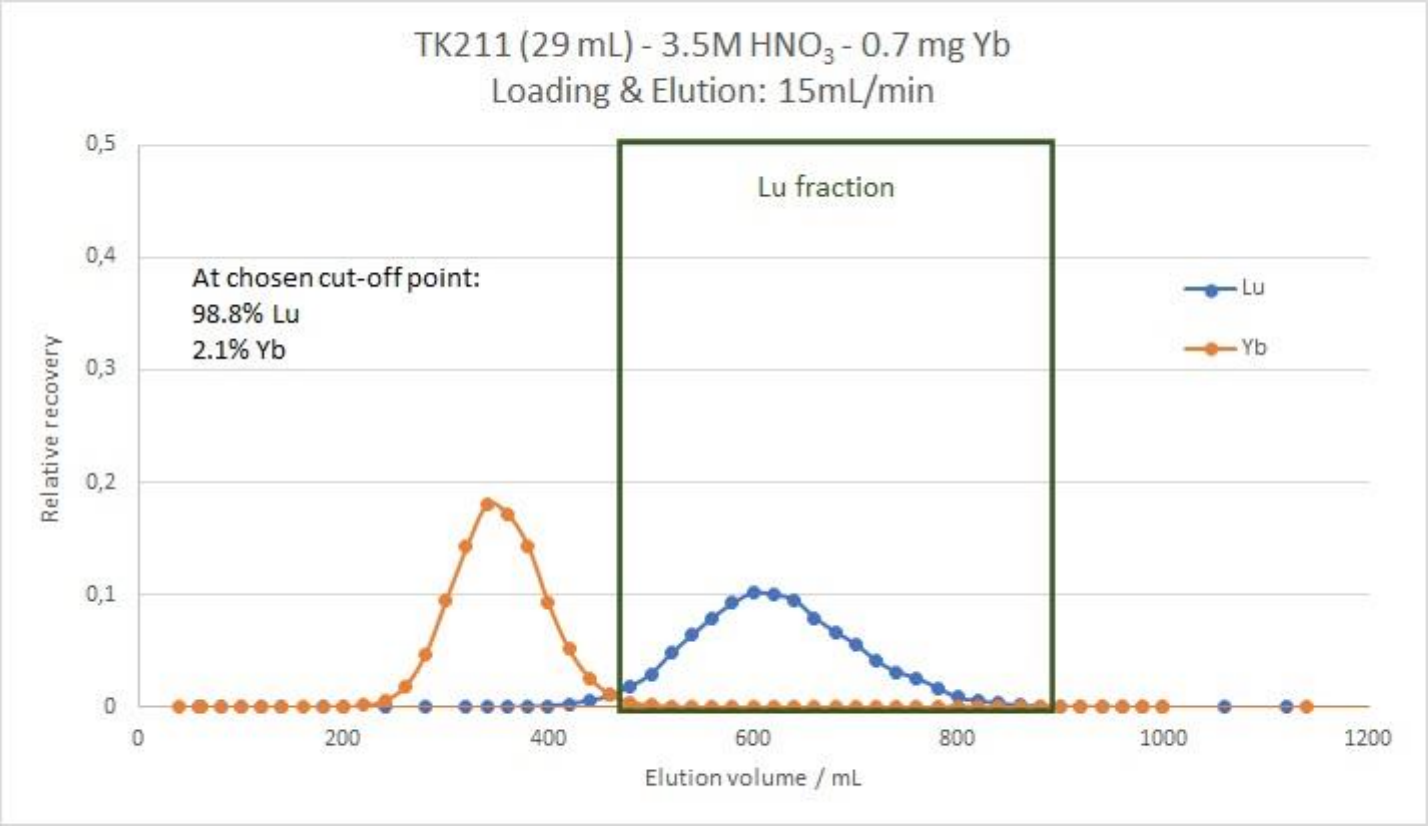
- Large tailing due to high Yb content
- Improved separation through use of 1.25M HNO_3 / 10% EtOH (v/v) instead of 1.3M
- Additional benefit from use of EtOH => improved radiolysis stability
- Online separation: switch at start of ‘Lu fraction’ => ideally radiation detector driven
- General aim: ~95% Lu recovery, ~80% Yb removal

Lu separation form 500 mg Yb - TK212/TK221/**TK212**/TK211



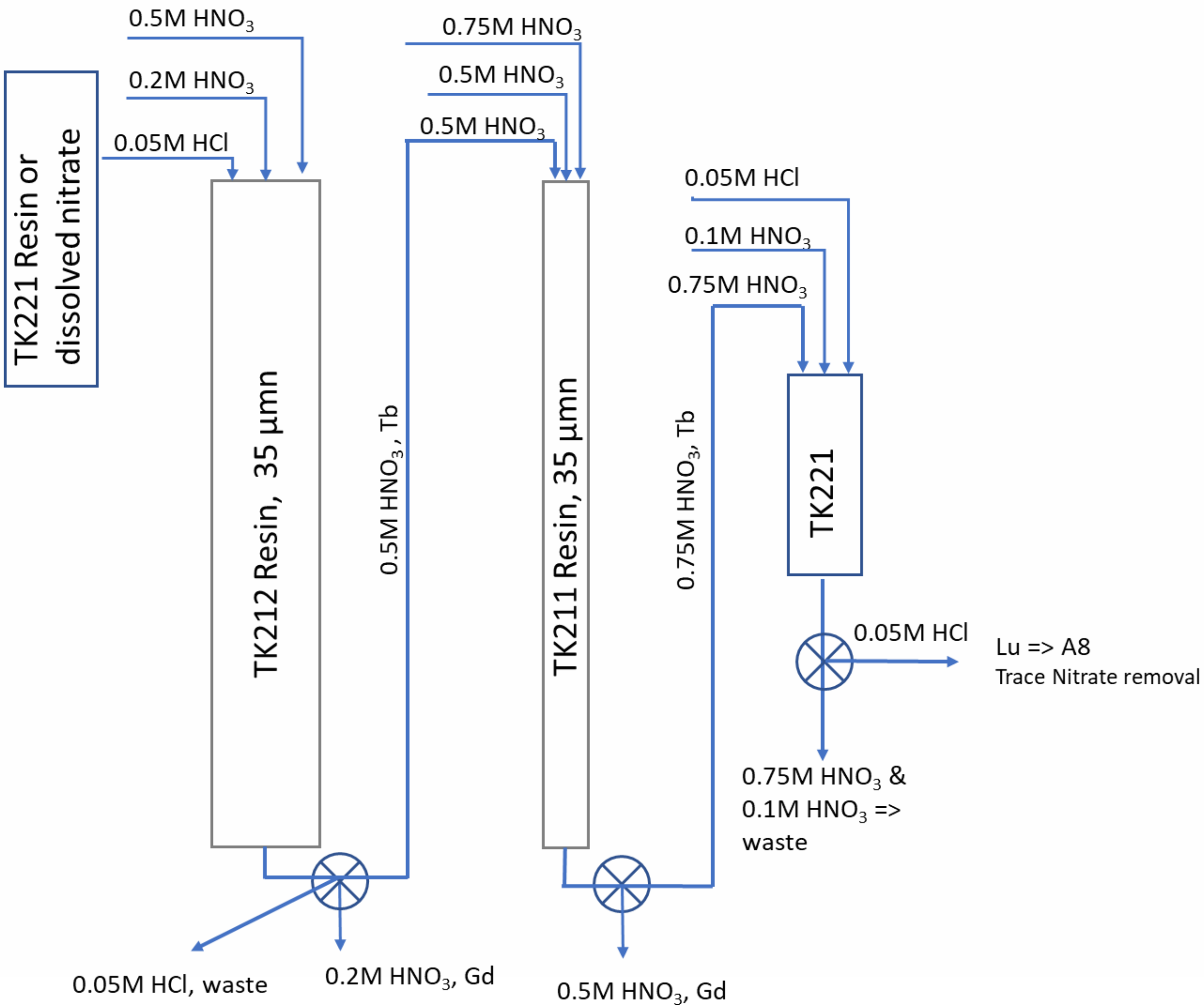
- 2nd separation step on smaller TK212 (53 mL) after TK221 for conversion from high HNO_3 to dilute HCl => 5g TK221
- Separation with e.g. 1.25M HNO_3 (with or without 10% EtOH)
- Generally aim: Lu >90% recovery, ~99% Yb removal
- Direct loading of obtained Lu fraction onto TK211 Resin
  - Alternatively TK221/TK212 according to Horwitz et al.

Lu separation form 500 mg Yb - TK212/TK221/TK212/**TK211**



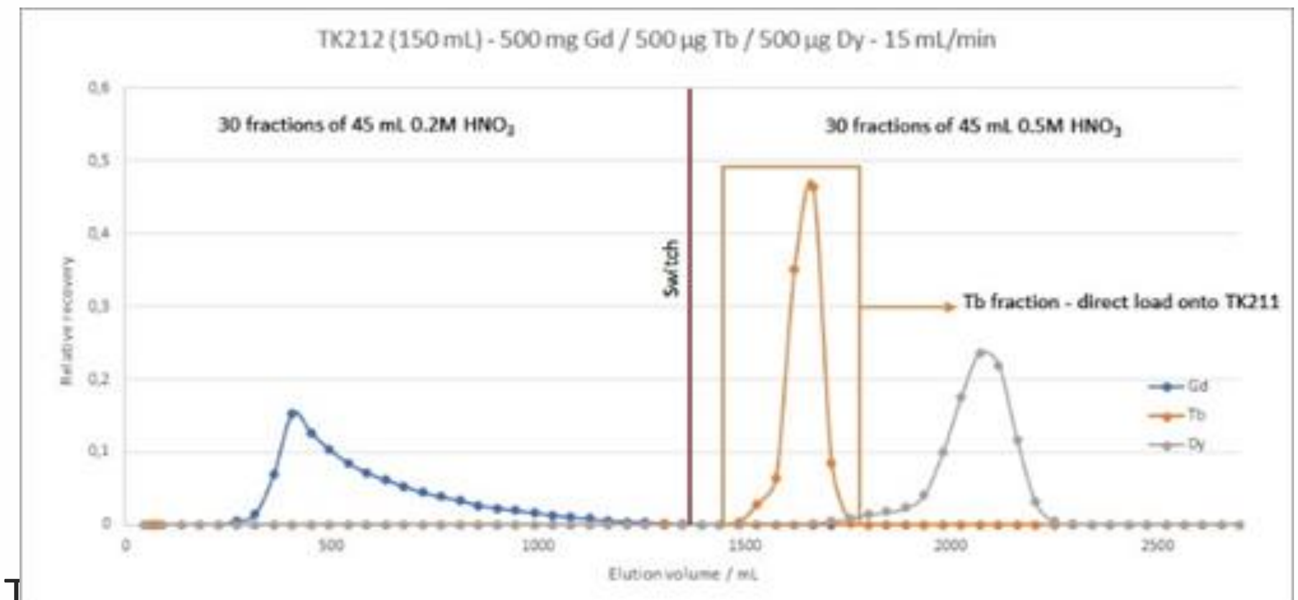
- Overall Lu recovery of process in the order of 85% => higher if more Yb allowed in final Lu
- Low remaining Yb
- Flow rates may still be optimized
- Final step: concentration/conversion to ≤ 0.05M HCl on TK221, nitrate removal via A8

Simplified method for Tb separation from 500 mg Gd – TK211/2 & TK221

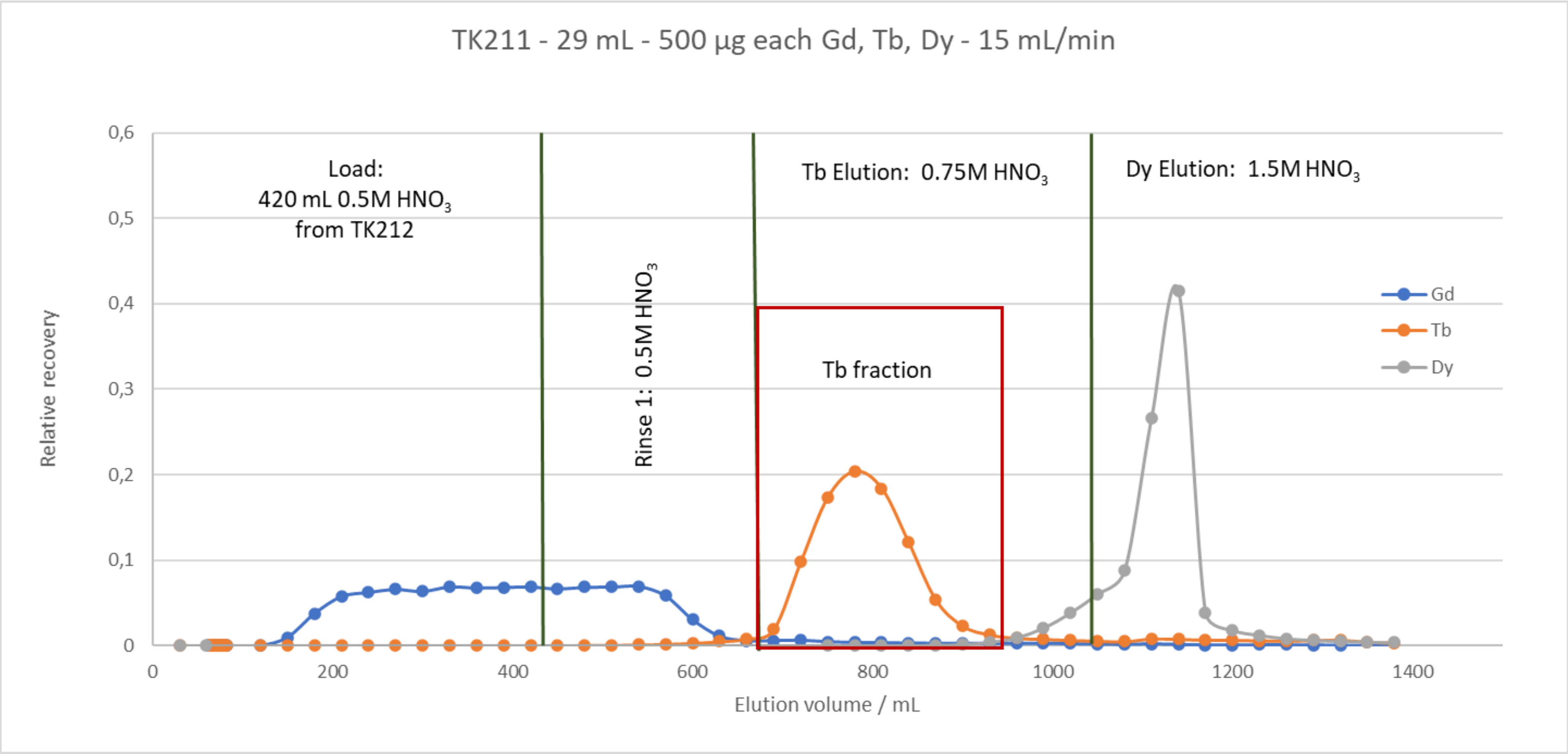


Tb separation from 500 mg Gd targets

- « Sequential separation » TK212 => TK211
- Initial separation on TK212 (150 mL column)
- Fine tuning ongoing (e.g. adjustment of eluents to 10% EtOH)
- Separation easier than Lu/Yb
- Polishing via direct load onto TK211 (29 mL)



Tb polish on TK211



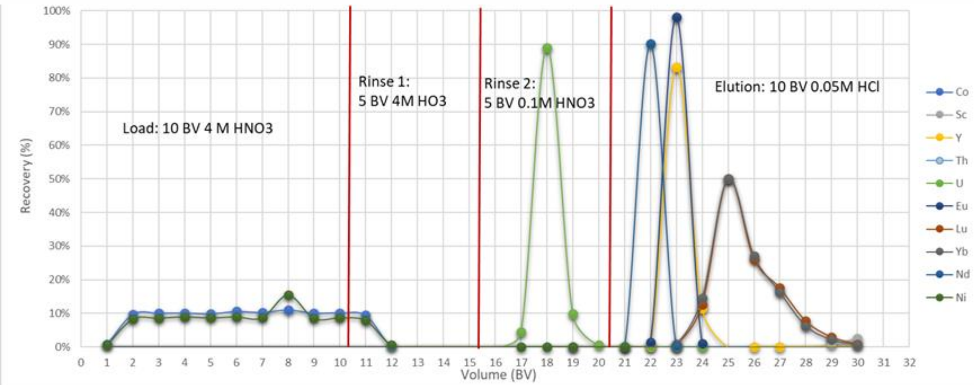
- Gd breaktrough during load & rinse with 0.5M HNO_3
- Method optimisation on-going => yields and purity very high
- Alternatively: Tb elution with 1M HNO_3

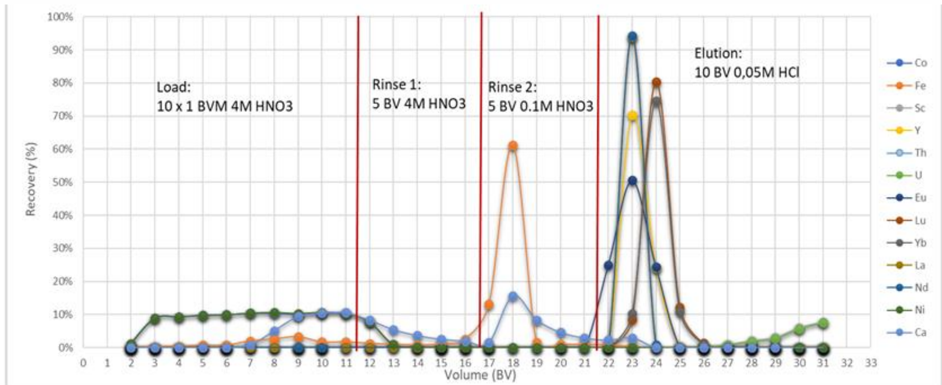
  => smaller elution volume / better Tb retention on TK221
- Conversion to dilute HCl via TK221, A8 for nitrate removal
- Next steps => Upscale to 1g and 2g of Gd

• On-going developments Lu-177 – new TK221 Resin

TRISKEM
Expertise in Separation Chemistry

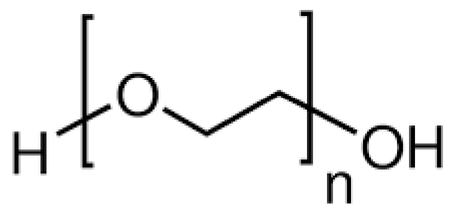
- DGA well suited for ‘conversion’ and purification (Ca, Al, Fe,… removal)
  - Convert Lu from high nitric acid to dilute HCl
- Elution of heavy lanthanides in 0.05M HCl needs elevated volumes
  - smaller volume prefered => higher activity concentration
- Optimisation of DGA Resin => new TK221 Resin
  - Lu eluted in smaller volume
  - Radioanalytical applications: higher U retention compared to DGA





Other ongoing R&D

- TK202 Resin
  - Based on Polyethylene Glycol (PEG) grafted on inert support
    - ➢ Presentation Izabela Cieszykowska



  - Poster presentation at ISTR2019, Vienna, 28/10/19 – 01/11/19
    - Tc recovery > 90% for 6 – 8g Mo per g of TK202
    - Tc recovery > 80% for 12g Mo per g of TK202
  - On-going tests:
    - Tc separation from larger Mo targets
    - Use of carbonate rinse for better pH control of eluate
    - Use of an aluminium oxide 'guard column' for trace Mo removal
    - Decommissioning => Tc determination in decommissioning samples after alcaline fusion => presentation A. Bombard
- SE Resin
  - Functional group covalently bound onto polymer support
  - Piazselenol chemistry (retention as Se(IV))
  - Load from e.g. 2M HCl, elution with 0.1M NaOH/0.1 H_2O_2
  - Se-72 separation and generator support, Se-79, Se isotope ratios

  => First beta testing on-going

Some other on-going projects

- Decontamination
  - PAN based resins,…
- Cs/Rb separation (TK300)
  - Beta testing on-going
  - Calixarene based
  - Probably 2 resins
- Ra Resin
  - Macrocycle based
  - Probably 2 resins
- Li Resin
  - Macrocycle based
- Rapid tests
  - Test sticks => Uni Southampton
  - DGA Sheets (2D TLC)
  - Extractive membranes
- At separation (TK400,…)
- Range of PSm based resins
  - TK-ElScint (p.ex. TK-TcScint)
- DGT (Diffusive Gradients in Thin Films) => 'bio-availability'
- Functionalised polymers & silicates,…
  - e.g. DO-DGA, DE-DGA, macrocycles,…
- Microfluidics
- Improvement of radiolysis stability
- Other types of supports

R&D coperations

- If any of these R&D topics are of interest – we are always looking for research collaborations or common projects so please contact us! => shappel@triskem.fr
- In case you have developed a new product that might be of interest please get in touch to discuss
- Please never hesitate to contact us if you have any technical questions or facing the need to develop new separations

Thank you for your attention!

TRISKEM
Expertise in Separation Chemistry